AC

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,404	02/13/2004	Roger K. Sunahara	UM-08794	7762

7590 11/08/2005

Tanya A. Arenson
MEDLEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,404	SUNAHARA ET AL.	
	Examiner	Art Unit	
	Kagnew H. Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *03 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Applicant's response on July 25, 2005 to the Office Action mailed on April 22, 2005 is acknowledged. Claims 1, 3, 12-14 have been amended. Claims 16-20 have been cancelled. Claims 1-15 are presently under consideration.

Priority

Priority from provisional application 60/447,074 tiled on 02/13/2003 has been acknowledged.

Maintain - Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 10 remains rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The rejection was explained in the previous Office Action.

Applicants argue: "The Applicants submit that they have provided a specific and substantial use for the enzyme of Claim 10 in the form of the assay described in Claim 1. The fact that the mutant enzyme is not found in nature is not relevant to its use in the methods of the present invention. One skilled in the art would recognize that the enzyme described in Claim 10 finds use in the screening of test compounds for their effect on nucleotide cyclase activity (e.g., for research or therapeutic uses) as well as structure function studies. As such, the Applicants submit that Claim 10 is supported by a specific and substantial utility and request that the rejection be withdrawn."

Given that there are at least two types of nucleotide cyclases with two distinct substrate specificities, it is not clear how a mutant nucleotide cyclase having altered substrate specificity could be of real world use in the assay as it is not clear how a compound identified by the assay

has any use. Applicants recite that the VC1-ACGC mutant cyclase has use in research or therapy, however the specification does not substantiate the uses of such a mutant in any type research endeavor or any therapy for any specific disease. As such identifying compounds, which modulate this enzyme, is not substantiated as the modulation identified has no real world use beyond studying the properties of the mutant cyclase itself (see MPEP 2107.01). Therefore the rejection is maintained.

Withdrawn - Claim Rejections - 35 USC § 112

The rejection of claims 1-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn following the amendments to the claims.

Maintain - Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection was explained in the previous Office Action.

3. Applicants argue "The Examiner has further rejected Claims 12-14 as allegedly being indefinite for the phrases "suspected ligand" "suspected activator" and "suspected inhibitor." In particular, the Examiner states "It is not certain what applicants intend or what qualities they refer by the recitation 'suspected'." (Office Action, pg. 4) The Applicants respectfully disagree and submit that the claims are definite as written. Nonetheless, in order to further the business

interests of the Applicants and while reserving the right to prosecute the original (or similar) claims in the future, the Applicants have amended claims 12, 13, and 14 to refer to a compound suspected of being an activator, ligand or inhibitor. As such, the Applicants submit that the Claim are definite and respectfully request that the rejection be withdrawn".

4. However the rejection remains maintained because applicant's amendment does not further clarify the claims. The issue is on what bases a person of skill in the art suspects a compound to be an activator, ligand or inhibitor. Applicants have not clarified the term by providing any structural and/or functional bases for the selection. Furthermore claim 1 from which claims 12-14 depend on is a method of screening test compounds for the ability to modulate nucleotide cyclase activity without reference to any compound. A screening method wherein the compound is any potential activator, ligand or inhibitor is encompassed in claim 1. However claim 12-14 drawn to a compound suspected of being an activator, ligand or inhibitor without clarifying the criteria for suspecting any particular compound of being a suspected activator, ligand or inhibitor. Therefore the rejection under 35 U.S.C. 112, second paragraph is maintained.

Maintain - Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 4-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claim 1 is incomplete without a control reaction (a reaction without the test compound) since it is critical or essential to the practice of the invention, but not

included in the claim(s) therefore is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). When examining the level of activity of any enzyme challenged with a test compound(s) one needs to also determine the level of enzyme activity in the absence of the test compound, thus the difference between the activity of the enzyme in the presence and absence of the test compound would reflect the net effect of the test compound on the activity of the enzyme. Claim 1 and dependent claims 4-15 are incomplete and are therefore not enabled.

Applicants argue:

> "The, Applicants submit that the absolute measure of fluorescence activity has meaning in determining the effect of a test compound on cyclase activity. The control reaction is not critical or essential to practice the invention. The Examiner has pointed to no evidence to the contrary. The Applicants have taught one of skill in the art how to practice the method of claim 1 as required under 25 U.S.C 1 12, first paragraph. Accordingly, the claims are enabled and the rejection should be withdrawn".

However applicant's argument is not found persuasive. Identification of a compound having the ability to modulate nucleotide cyclase activity by using a fluorescent substrate in a reaction cannot be accomplished without knowledge of the amount of fluorescence in the absence of a test compound (i.e. the intrinsic fluorescence), as one could not determine if anything has changed without such knowledge.

Withdrawn - Claim Rejections - 35 USC § 102

Applicants correctly point out the use of the reference by Gille et al. as cited in the previous Office Action and in Form 892 does not constitute prior art. The Gilles et al reference cited and provided in the previous office action is erroneous. Thus the 102(a) rejection with regards to said reference is withdrawn. However the reference provided herewith by the same authors i.e. Gille et al applies to the rejection under 102(a).

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5, 6 and 14 rejected under 35 U.S.C. 102(a) as being anticipated by Gille et al. (Gille et a1. 2'(3')-o-(N-Methylanthraniloyl)-substituted GTP Analogs: A Novel Class of Potent Competitive Adenylyl Cyclase Inhibitors. Journal of Biological Sciences Vol. 278, No15, pp12672-12679) which first appeared on line on February 3rd, 2003). Claims 1, 5, 6 and 14 rejected under 35 U.S.C. 102(a) as being anticipated by Gille et. al. who disclose fluorescently labeled GTP analogs that are potent adenylyl cyclase inhibitors and a method of assaying adenylyl cyclase (AC) activity in the presence of 5mM $MgCl_2$ or in the presence of 10mM $MnCl_2$ and 100mm forskolin (an activator of AC activity) and a fluorescent GTP analog MANT-GTPyS thus Gille et. al.'s method encompasses the method steps disclosed by applicants, hence anticipates claims 1, 5, 6 and 14. Given that the priority date of this Gilles et al reference is prior art as indicated above, the rejection under 35 U.S.C. 102(a) applies.

Withdrawn - Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 9, 11-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Dieter et al (US PAT 6323186 B 1). Dieter et al disclose a method of fluorescent assay including protein binding assays and hydrolase enzymes which include nucleotide cyclases. A method of analyzing enzyme activity in a sample containing fluorescent GTP derivatives that encompasses BODIPY-FL-GTPγS as a substrate is disclosed, thus anticipating claims 1- 9, 12, 13, 1 5. Furthermore, a kit containing said substrate, an enzyme that hydrolyses the substrate inhibitors (claim 14) and a high throughput screening method, including micro-well plates or micro-fluidic chips (anticipating claim 11, 16-1 8 and 20) are disclosed. Therefore, Dieter et al anticipate the claimed inventions in claims 1- 9, 1 1-18 and 20.

Upon further consideration although the fluorescent substrate to be used in the method of applicant's invention in claims 1- 9, 11-18 and 20 is identical to the BODIPY-FL-GTPγS used in Dieter et al, the nucleotide cyclase used in the method of the present invention is not encompassed by Dieter et. al's invention because the nomenclature in the art does not classify nucleotide cyclases as being encompassed by nucleotide hydrolases. Therefore the rejection of claims 1- 9, 11-18 and 20 under 35 U.S.C. 102(b) as being anticipated by Dieter et al has been withdrawn.

Withdrawn-Claim Rejections - 35 USC § 102

The rejection of claims 1-3, 5, 9, 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Rossomando et. al. (Proc. Natl. Acad. Sci. USA Vol 78, No. 4 pp. 22782282, 1981) has been considered and found applicant's arguments to be persuasive with regard to a rejection under 35 U.S.C. 102(b). Therefore this has been withdrawn. However claims 1-3, 5, 9, 12-15 of applicant's invention are obvious over Rossomando et al's teaching as indicated below.

Maintained - Claim Rejections - 35 USC § 103

Claims 1-9, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et. al in view of Gilles et al. As indicated above, Gilles et al first appeared on line on February 3rd, 2003, therefore Gilles et al's teaching is prior art contrary to applicant's argument. Applicant's have not responded to the rejection under 35 U.S.C. 103(a) therefore the rejection is maintained.

Withdrawn - Claim Rejections - 35 USC § 103

8. Claims 1-9, 11-15 rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et. al in view of McEwen et al has been withdrawn. Applicant's argument has been carefully considered and have been found persuasive in that the Herr reference in combination with the McEwen reference alone does not fully satisfy a rejection under 35 U.S.C. 103(a). McEwen et al teaches the use of fluorescent BODIPY-FL-GTPγS binding to G protein subunit(s) rather than to nucleotide cyclases as is the case in the instant application and that there is insufficient motivation to combine the McEwen reference with the reference by Herr. Both references by McEwen found in applicant's IDS (1449) have been considered as acknowledged by examiner's signature. Additionally the specific reference by McEwen used in the rejection under 35 U.S.C. 103(a) is provided by the examiner. Examiner apologizes for the confusion regarding which one of the references was used in the previous Office Action.

Maintained - Claim Rejections - 35 USC § 103

9. Claims 6 and 7 and now including 1-5, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et. al in view of Rossomando et al. further in view of McEwen et al.

Applicants argue "The Examiner has rejected Claims 6, 7, and 16-18 under 35 U.S.C. 103(a) as allegedly being obvious in light of Herr in view of Rossomando (Office Action, pg. 8). Claims 16-18 have been canceled for other reasons. Applicants note that the Examiner has only applied the instant rejection to dependent Claims 6 and 7. Applicants note that, by definition, Claims 6 and 7 include the elements of independent Claim 1. The Applicants submit that the Examiner has failed to provide a motivation to combine the teachings of Rossomando with the teachings of Herr. Herr is silent on the use of fluorescent-based methods of assaying test compounds. Indeed, Herr indicates that suitable methods are known in the art for assaying adenyl cyclase activity: "CAMP production may be readily measured using methods which are well known in he art. . ." (paragraph 0059). Herr does not indicate any deficiencies in the art known assay methods. Nor does Herr indicate the need for alternative assay methods. Likewise, McEwen does not suggest that the disclosed fluorescent nucleotide analogs find use in the assay of soluble or orphan nucleotide cyclase enzymes as required by Claims 6 and 7. The Examiner's basic argument appears to be that because the methods of Rossomando could, in theory, be applied to Herr that one would be motivated to make the combination. As described above, this is not the proper standard for obviousness rejections. The Applicants further submit that the Examiner has used improper hindsight reconstruction (See above description). "

2. Applicant's argument has been fully considered but not found persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The teaching by Rossomando et al clearly articulates the need for the use of fluorescent nucleotide analogues in adenylate cyclase reactions to avoid problems of radioactive waste disposal [see page 2281, second column 2nd paragraph]. Various nucleotide analogues including

BODIPY-FL-GTPγS are taught by McEwen et al. Thus it would have been obvious for a person of ordinary skill in the art to apply any fluorescent nucleotide analogue in a reaction involving any nucleotide cyclase enzyme as suggested by Rossomando et al.

Applicant argues "The Applicants further submit that neither Rossomando nor Herr alone or in combination, teach all of the elements of the claims as required for rejection under 35 U.S.C. 103. For example, neither Rossomando nor Herr, alone or in combination, teach the claim elements of an orphan receptor as required by Claim 7. The Applicants submit that the Examiner has failed to provide a prima facie showing of obviousness. As such, the rejection should be withdrawn".

However this is not found persuasive. The motivation for using a fluorescent nucleotide analogue and fluorometry in a nucleotide cyclase reaction is clearly stated in Rossomando et al. thus Rossomando's teaching is very clear in the use of a fluorescent nucleotide analogue not only in adenylate cyclase reactions but in any ATP or cAMP-dependent reaction [see page 2281, second column 2nd paragraph]. The fact that Herr et al is silent on the use of fluorescent-based methods is irrelevant since it is the combination of both the cited references that need to be considered. Thus the combination of disclosures by Herr et al in and Rossomando et al clearly suggests to one of ordinary skill in the art the use of a screening assay designed to identify agonists, inhibitors or binding proteins (Herr et al) using fluorescent nucleotide analogue in nucleotide cyclase reactions by avoiding problems associated with radioactive waste disposal (Rossomando et al). Thus claims 1-9, and 15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Herr et. al in view of Rossomando et al. further in view of McEwen et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kagnew Gebreyesus PhD.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600